Ethnopharmacology, phytochemistry and pharmacology of the Genus *Hedyosmum* (Chlorantaceae): a review

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Abstract

Ethnopharmacological relevance: The genus *Hedyosmum* (family: Chloranthaceae) represents an interesting source of natural active compounds from 45 species that are widespread in Central and South America and Southeast Asia. Several species of the genus *Hedyosmum* have been reported for their aerial distribution and traditional use in folk medicine mainly in several Countries of Central and South America, and Southeast Asia to a lesser extent (south China and West Malaysia). However, data made available in recent years have not been organized and compared.

Aim of this review: The aims of the present study is a critical assessment of the state of the art concerning the traditional uses, the phytochemistry and the pharmacology of species belongings to the genus *Hedyosmum*, in order to find suggestions for further specific researches strategies and exploit the therapeutic potential of the *Hedyosmum* species for the treatment of human disorders.

Materials and methods: The present review consists in a systematic overview of scientific literature concerning *Hedyosmum* genus published between 1965 and 2018. Moreover, has been reported a very ancient text concerning *H. bonplandianum* Kunth traditional uses which is dated 1843. Several databases (Francis & Taylor, Google Scholar, PubMed, SciELO, SciFinder, Springer, Wiley, The Plant List Database) have been used in order to perform this work.

Results: 16 species of the genus *Hedyosmum* have been mentioned as traditional remedy and a wide number of ethnomedicinal uses has been reported, including the treatment of pain, depression, migraine, stomach and ovary diseases. 5 species have been reported for their use as flavoring agent, tea substitute or food. Sesterterpens, sesquiterpene lactones, monoterpenes, hydroxycinnamic acid derivatives, flavonoids and neolignans have been reported as the most important components and several researches have shown that the *Hedyosmum* genus possess active compounds with promising biological properties such as: analgesic and antinociceptive activities, antidepressant activity, anxiolytic, sedative and hypnotic effects. Preliminary studies concerning antibacterial, antioxidant, antiplasmodial, antifungal and cytotoxic activity against different tumor cell lines have been reported. Some active compounds from *Hedyosmum* genus have been used as starting points for innovative bioinspired synthetic molecules. A critical assessment of the papers reviewed has been performed and some conceptual and methodological problems have been identified regarding materials and methods and the experimental design, including also the lack of ethnopharmacological research. The assessment was based on the recent guidelines for manuscript submission in the peer-reviewed pharmacological literature.

Conclusions: the present review allows to partially confirming some traditional uses of *Hedyosmum* species (mainly *H. brasiliense*) by preclinical studies, such are antinociceptive and neuroprotective effects. The pharmacological effects of this genus can be mainly attributed to the presence of sesquiterpenes, sesterterpenes and hydroxycinnamic acid derivatives. Due to preliminary promising results, new studies concerning 13-hydroxy-8,9-dehydroshizukanolide and podoandin should be the subject of additional research. Moreover, several essential oils (EOs) from the genus have been studied and the cytotoxic and antibacterial activity of *H. brasiliense* and *H. sprucei* EOs deserve more investigation. From the results of the present investigation this genus certainly deserves further researches on the ethnopharmacology and the toxicology fields.

Keywords: *Hedyosmum*, traditional uses, Phytochemistry, Pharmacology.

Abbreviations

DPPH	α, α-diphenyl-β-picrylhydrazyl Antioxidant activity essay
EOs	Essential Oils
GI_{50}	Cell growth Inhibition by 50%
IC_{50}	Inhibitory concentration 50%
VERO	Green monkey kidney cells
MCF-7	Human breast cancer cells
THP-1	Human leukemia monocyte cell line
A-549	Human lung carcinoma
DLD-1	Human colon adenocarcinoma
BQ-123	ETA antagonist (endothelin-1 ETA receptor)
13HDS	13-hydroxy-8,9-dehydroshizukanolide
PDA	Podoandin
FST	Forced swimming test
ARD	Aromadendrane-4β,10α-diol
HDS	13-hydroxy-8,9-dehydroshizukanolide
BHT	Butylhydroxytoluene
BHA	Butylhydroxyanisole
ORAC	Oxygen radical absorbance capacity
TEAC	Trolox equivalent antioxidant capacity (weak anti-tyrosinase).
A-549	Human lung cancer cell line
HL-60	Human leukemia cells (tumor cell lines)
LD_{50}	Medium Lethal Concentrations value
HPTLC	High performance thin layer chromatography
MCF-7	human breast cancer cell line
NSCLC	non-small-cell lung cancer cells
NF-κB	Nuclear factor κB
PS-341	inhibitor of the proteasome

1. Introduction

The genus *Hedyosmum* (Chlorantaceae) includes 48 species of small trees or shrubs (45 of which taxonomically characterized, as *accepted*, 3 species *unresolved* that mainly means that they are not still knowable as *accepted* or *synonyms*) (The Plant List Database). The mentioned species are widespread in low and high mountain rain forests like the Andes of South America (Ecuador, Peru, Brazil central part of Bolivia) and the mountains of southern Mexico and Central America (Zhang et al. 2016; Guerrini et al. 2016). It is the most abundant genus belonging to the Chlorantaceae family in America (Kirchner et al. 2010). *H. orientale* has been reported in China and West Malaysia. These plants present strong fragrance as a common characteristic, indeed, the genus name finds its origin in the Greek words *hedy*- (sweet, nice, fragrant), and *osme* (smell). The Chlorantaceae family includes the genera *Sarcandra* (2 accepted species), *Chloranthus* (14 accepted species)*, Hedyosmum* (45 accepted species) and *Ascarina* (12 accepted species). This family, considered as one of the most primitive among Angiospermae, shares the presence of secretory cells in the stems and leaves as common characteristic (Kirchner et al., 2010; Eklund et al., 2004)).

The genus is characterized by unisexual diclinous flowers and dentate and opposite leaves, with petioles sheathed on the base (Todzia, 1988). The genus is characterized by unisexual diclinous flowers and dentate and opposite leaves, with petioles sheathed on the base (Todzia, 1988).

There are reports attesting the use of aerial parts (mainly leaves, but also bark and fruits) of species belonging to the genus *Hedyosmum* in ethnomedical practices and traditional medicines, mainly related to south and Central America populations. Moreover, a consistent number of studies in the scientific literature concern the chemical characterization of all the different parts of the plant – all strongly aromatic - and biological activities of corresponding derivatives that encourage uses of these plants in the cosmetic or medicinal field.

Therefore, due also to the wide presence of this genus in several countries and to the ethnobotanical/ethnomedical importance of many species belonging to this genus, further studies are needed in order to evaluate their potential applicative healthy uses.
The aim of this review is to provide a critical analysis of the state-of-the-art concerning the ethnopharmacology, phytochemistry, pharmacology and toxicology (with particular attention to cytotoxic effects) regarding extracts and isolated compounds belonging to the genus Hedyosmum. Moreover, the authors will suggest which further specific studies are needed and which is the therapeutic potential of the Hedyosmum specie for the treatment of human diseases.

2. Materials and methods

A detailed bibliographic study was performed including papers from the year 1965 to 2018. 112 documents have been evaluated at the beginning and from these data have been selected 50 references concerning ethnopharmacology data, phytochemistry and pharmacology studies of the Genus *Hedyosmum*, 14 additional papers have been used in order to complete the present manuscript.
45 plant species were mentioned according to the classification of the web page www.theplantlist.org and 28 synonyms were identified. Three species remains still unresolved that mainly means that they are not still knowable as accepted or synonyms Focusing on data obtained from theplantlist.org, as keywords were selected: the name of the genus, all the scientific name of the species belonging to genus *Hedyosmum*, all synonyms of the above mentioned scientific names.
The present review was carried out adopting the following electronic databases: Francis & Taylor, Google Scholar, PubMed, SciELO, SciFinder, Springer, Wiley. The authors checked also the pharmacopoeias of Latin America or Central America countries but no data concerning *Hedyosmum* genus have been found.
Only articles have been included and were avoided data from symposiums, patents, and congress abstracts because not enough complete to warrant an effective comparison with full papers.
Due to the lack of data concerning the traditional uses, some thesis were initially checked but were rejected because considered unreliable from the scientific point of view.

3. Traditional uses.

The oldest reference found in the present review article is dated 1843, is Latin written and mentions the traditional use of *H. bomplandianum* leaves infusion as a febrifuge and analeptic remedy, also useful against hemicranias and pain inflicted by a cold (Martius, 1843). The most relevant reference concerning *Hedyosmum* genus traditional uses is the "Dictionary of Trees. Volume 2. South America. Nomenclature, Taxonomy and Ecology", (Grandtner and Chevrette, 2014). 18 *Hedyosmum* species were mentioned as medicinal remedy or food source (beverage and fruits), some species has been also mentioned in order to produce firewood and for constructions.
The most reported traditional uses for the *Hedyosmum* genus are: sedative, aphrodisiac, antidepressant and stomachache sedative. *H. angustifolium* has been mentioned for relaxing infusion and tea substitute preparation, *H. anisodorum*, *H. arborescens*, *H. scaberrimus* and *H. scabrum* have been mainly reported as for digestive, antispasmodic and stomach calmer while *H. angustifolium*, *H. bonplandianum* and *H. racemosum* are used against soothe rheumatic and aching joints pains, fever and cold symptoms. *H. colombianum* and *H. cumbalense* traditional uses are mainly connected to human consumption as flavoring agents and, finally, *H. sprucei* has been reported as useful in the treatment of snake bites.
Traditional uses of *Hedyosmum* genus from different countries are listed in Table 1.
Especially throughout Central and South America, different *Hedyosmum* species have been used for a wide range of purposes; the main traditional preparation in folk medicine is a pleasant tea from leaves, which is offered as traditional remedy. Also bark and fruits have been reported for medicinal traditional uses or as a pleasant food, in many cases the infusions of different *Hedyosmum* species have been mentioned as aromatic beverages (Todzia, 1988).
Table 1 emphasizes that *H. brasiliense* is the most mentioned species: in fact, most of the listed traditional uses for this plant concern the Brazilian territory. Detailed examples of the preparation procedures concerning the traditional uses are poorly reported. However, infusion of aerial parts has been the most mentioned folk medicine products and is used both for ingestion or topical application; also home-distilled alcoholic beverages have been reported as traditional remedy.

The species of the genus *Hedyosmum* have different synonyms, as shown in Table 1, and they are extensively widespread in several countries, as shown in Figure 1. In addition, the common names are characteristic of the regions where they come from. In Bolivia, *H. angustifolium* (Ruiz & Pavón) is called “Matico menta”, in Brazil can be reported the case of *H. brasiliense*, which is known as "cidrão", "cidreira" and "erva-de-bugre", among other names. In Colombia, the *H. translucidum* Cuatrec is known as "Granizo" or "Granicillo", because of the shape of its fruits. In Ecuador *H. scabrum* is known as “Guayusa de cerro”, “Tarqui” or “Graniso”, (De la Torre et al.,, 2008); *H. sprucei*, it is known as "sacha limón panga", " sacha limón caspa," or " hoja de monte” (Guerrini et al.,, 2016).

Figure 1 – Geographical distributions of the most abundant *Hedyosmum* species.

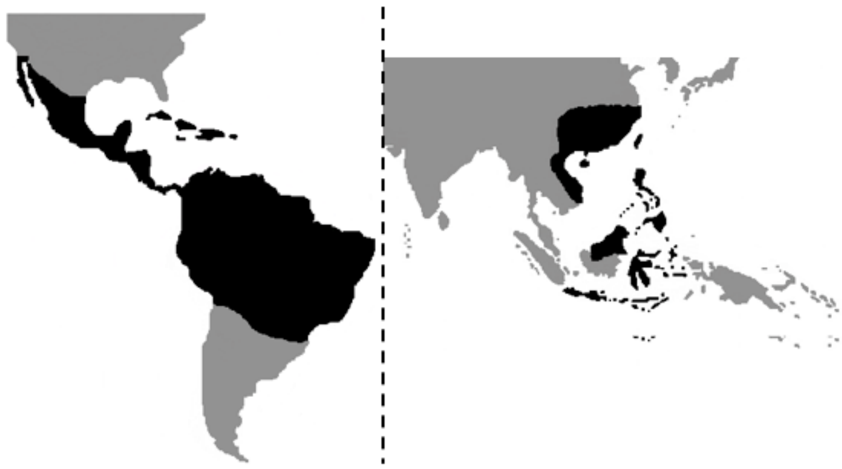


Table 1 – Ethnobotanical information regarding the species belonging to the genus *Hedyosmum* known for their traditional uses (Botanical names and synonyms are reported according to The Plant List Database; http://www.theplantlist.org/)

Species	**Synonyms**	**Traditional medicinal uses**	**Used part**	**Traditional preparation procedures**	**Distributions**	**Reference(s)**
H. angustifolium (Ruiz & Pav.) Solms	*H. laciniatum* (Ruiz & Pav.) Solms *H. pavonii* (Solms) Diels *H. scabrum* var. *pavonii* Solms *Tafalla angustifolia* Ruiz & Pav. *Tafalla laciniata* Ruiz & Pav.	Antirheumatic, cold treatment	Leaves	NA	Bolivia	Lorenzo et al. (2006)
		Relaxing infusion, tea substitute	Leaves	Infusion	Ecuador, Perù, Bolivia	Grandtner and Chevrette (2014)
H. anisodorum Todzia	No synonyms (accepted specie)	Stomach pain	Mature Fresh Leaves	Infusion	Ecuador	Todzia (1988)
		Infusion	Leaves	Infusion	Euador, Perù	Grandtner and Chevrette (2014)
H. arborescens Sw.	*H. elegans* Cordem. *Tafalla arborescens* (Sw.) Kuntze	For digestive, cold treatment, antispasmodic	Leaves	NA	Guadeloupe, French West Indies	Bercion et al. (2005)
H. bonplandianum Kunth	*H. callososerratum* Oerst. *Tafallaea bonplandiana* (Kunth) Kuntze *Tafallaea callososerrata* (Oerst.) Kuntze	Tranquilizer, hypnotic, analgesic, febrifuge	Leaves	NA	Panama Colombia	Caballero-George et al. (2001) Cárdenas et al. (1993)
		Febrifuge, analeptic for the treatment of hemicranias and pain inflicted by a cold	Leaves	Infusion	Brasil	Martius (1843)

		Febrifuge	Bark	NA	Nicaragua, Panama, Colombia Ecuador	Grandtner and Chevrette (2014)
H. brasiliense Mart.	*H. acutifolium* Cordem. *H. grandifolium* Occhioni *H. weddellianum* Cordem. *Tafalla brasiliensis* (Miq.) Kuntze *Tafalla weddelliana* (Cordem.) Kuntze	Febrifuge, chills, and migraine pains, diuretic, stomach calmer, for ovaries diseases, rheumatism, sedative, antidepressant, hypnotic, aphrodisiac, foot fungi treatment, general refresher and substitute of green tea.	Leaves	Infusion	Central and South America, Brazil	Todzia (1988) Reitz (1965) Calixto et al. (2001) Trentin et al. (2015) Uphof (1968)
H. colombianum Cuatrec.	No synonyms (accepted specie)	Odoriferous, flavoring substance in food	Leaves	NA	Colombia	Delgado et al. (2010)
H. costaricense C.E.Wood ex W.C.Burger	No synonyms (accepted specie)	NA	NA	NA	NA	
H. crenatum	No synonyms (accepted specie)	Infusion againt flu	Leaves	Infusion	Colombia, Venezuela	Grandtner and Chevrette (2014)
H. cuatrecazanum Occhioni	*H. crassifolium* Urb.	Infusion against kidney illness, aromatic water	Leaves	Infusion	Colombia, Venezuela, Ecuador, Perú, Bolivia	Grandtner and Chevrette (2014)
H. cumbalense	No synonyms (accepted specie)	Flavoring agent	Leaves	NA	Central and South America	Todzia (1988)
		Against stomachache	Leaves	Infusion	Colombia Ecuador, Perú	Grandtner and Chevrette (2014)

H. goudotianum Solms	*H. goudotianum* var. *goudotianum* *H. montanum* W.C.Burger *Tafallaea goudotiana* (Solms) Kuntze	Infusion against stomachache	Leaves	Infusion	Costa Rica, Panamá, Colombia, Venezuela, Ecuador, Perú	Grandtner and Chevrette (2014)
H. luteynii Todzia	No synonyms (accepted specie)	Infusion against kidney diseases	Leaves	Infusion	Colombia, Ecuador Perù	Grandtner and Chevrette (2014)
H. maximum	No synonyms (accepted specie)	Stimulant infusion	Leaves	infusion	Peru, Bolivia	Grandtner and Chevrette (2014)
Hedyosmum mexicanum C.Cordem.	*H. artocarpus* Solms *Tafalla glauca* Ruiz & Pav. *Tafallaea artocarpus* (Solms) Kuntze *Tafallaea mexicana* (C.Cordem.) Kuntze	Food	Fruits, leaves	Infusion	Mexico, Panama, colombia	Grandtner and Chevrette (2014)
H. nutans Sw.	No synonyms (accepted specie)	Infusion with *Stenostomum lucidum* against colic	Leaves	Infusion	Guatemala, Belize, Honduras, Bahamas, Trinidad	Grandtner and Chevrette (2014)
H.orientale Merr. & Chun	No synonyms (accepted specie)	NA	NA	NA	NA	
H. purpurascens Todzia	No synonyms (accepted specie)	Food	Leaves	infusion	Ecuador	Grandtner and Chevrette (2014)
H. racemosum (Ruiz & Pav.) G.Don	*H. bolivianum* Cordem. *H. glabratum* Kunth *H. glaucum* (Ruiz & Pav.) C. Cordem. *H.huilense* Cuatrec. *H.integrum* Cordem. *H. llanorum* Cuatrec. *Tafalla integra* (Cordem.) Kuntze *Tafalla racemosa* Ruiz & Pav.	Aching joints treatment	Leaves	Infusion for external use	Central and South America	Todzia (1988)
		Bronchitis	NA	NA	Perú	Bussmann et al. (2010)

		Medicinal infusion	Leaves	Infusion	Colombia, Venezuela, Guyana, Ecuador: Peru, Brazil Bolivia	Grandtner and Chevrette (2014)
H. scaberrimum Standl.	No synonyms (accepted specie)	Medicinal infusion	Leaves	Infusion	Nicaragua, panama, Colombia, Ecuador	Grandtner and Chevrette (2014)
H. scabrum (Ruiz & Pav.) Solms	*H. hirsutum* Kunth *H. latifolium* Cordem. *H. mandonii* Solms *H. scabrum* var. *scabrum* *Tafalla mandonii* (Solms) Kuntze *Tafalla scabra* Ruiz & Pav.	Stomach calmer, fertility promoter	Leaves	Infusion	Central and South America	Todzia (1988)
		Cold treatment, antirheumatic	Leaves	NA	Bolivia	Lorenzo et al. (2003)
		Antispasmodic	Leaves	Infusion	Perù	De Feo and Soria (2007)
		Infusion against stomacache	Bark and leaves	Infusion	Colombia Ecuador,Peru, Bolivia	Grandtner and Chevrette (2014)
H. scabrum var. *pavonii* Solms	*H. angustifolium* (Ruiz & Pav.) Solms	NA	NA	NA	NA	
H. scabrum var. *scabrum*	*H. scabrum* (Ruiz & Pav.) Solms	NA	NA	NA	NA	
H. sprucei Solms	*H. flocculosum* Diels *Tafalla sprucei* (Solms) Kuntze	Snake bites	Leaves	Cooked poultice for external use	Central and South America	Todzia (1988)
		Medicinal infusion	Leaves	Infusion	Colombia, Ecuador, Peru	Grandtner and Chevrette (2014)
H. translucidum Cuatrec.	*No synonyms (accepted specie)*	Lemon-flavored infusion	Leaves	Infusion	Colombia Venezuela, Ecuador, Peru	Grandtner and Chevrette (2014)

H. uniflorum Todzia	*No synonyms (accepted specie)*	Medicinal infusion	Leaves	Infusion	Ecuador	Grandtner and Chevrette (2014)

NA – Not available

Infusion is the most mentioned traditional preparation procedure. Reitz (1965) reported a traditional preparation procedure, concerning *H. brasiliense*, in which 30 g of the fresh leaves are infused in 600 g of white wine, producing a tonic and aphrodisiac effects. Unfortunately (as showed in Table 1), no other detailed folk medicine procedures are reported and the other authors mentioned just general information concerning the used part of the plant or the extraction methods (e.g.: infusion, cooked poultice for external use, etc.)
Nowadays, no data are available regarding the validation of the traditional use of *Hedyosmum* genus extracts and no information are reported in the pharmacopoeias of Latin America or Central America countries, despite being the areas of greatest distribution and uses of the genus.
Additionally, there are not scientific studies concerning the synergistic effect with other species commonly used in the same countries where *Hedyosmum* genus is widespread. There is just a mention concerning the traditional use of an infusion of *Stenostomum lucidum* and *H. nutans* against colic.
In any case, there are very few ethnomedical data concerning the traditional preparation procedures or rituals, the used part of the plant and general traditional knowledge related to the *Hedyosmum* genus.

4. Phytochemistry

The main chemical constituents of *Hedyosmum* genus are listed in Table 3 and the chemical characterization of *Hedyosmum* species essential oils is summarized in Table 4.
There are interesting unique compounds in the *Hedyosmum* genus, such as Hedyosumin A, B, C, D, E and Hedyorienoid A and Hedyorienoid B. As reported by Trentin et al. (1999), 13-hydroxy-8,9-dehydroshizukanolide has been isolated from *H. brasiliense* and other plant species.
Sesquiterpenes and sesterterpenes represent the main relevant focus of several researches concerning the biological activities of *Hedyosmum* genus. Moreover, other interesting compounds as rosmarinic acid have been reported in order to understand the biological activities *Hedyosmum* genus. Detailed information is available also in Section 5.

4.1 Sesquiterpenes and Sesterterpenes

Sesterpens are the main studied components reported in the *Hedyosmum* genus and *H. brasiliense* is the most mentioned species. The presence of seven sesquiterpenes in the species *H. brasiliense* has been reported by Amoah et al., (2013): guaianolide podoandin, 1,2-epoxy-10a-hydroxy-podoandin, 1-hydroxy-10,15-methylenepodoandin, elemenolide 15-acetoxy-isogermafurenolide, 15-hydroxy-isogermafurenolide, lindenanolide 8α/β,9α hydroxyl-onoseriolide and onoseriolide. This last compound has been previously isolated from the *H. angustifolium* bark by Acebey et al., (2010) together with other sesquiterpenes as oxyonoseriolide, hedyosmone, chloranthalactone A and spathulenol.
Also Su et al., (2008) have been reported the presence of spathulenol, and other sesquiterpenes such as 13-hydroxy-8,9-dehydroshizukanolide and aromadendrane-4β,10β-diol from ethanolic extract of the *H. orientale* aerial parts. The sesquiterpene alcohol aromadendrane-4β,10α-diol was obtained from the leaves of *H. brasiliense* by Amoah *et al*. 2013a 2015b. The mentioned compound was previously separated from other plant species such as *Xylopia brasiliensis* (Moreira et al. 2003).
Amoah et al., (2013a; 2015b) recorded the eudesmane sesquiterpene lactones 1-α-acetoxyeudesma-3,7(11)–dien–8,12–olide and 15-hydroxy-isogermafurenolide from *H. brasiliense*. The sesquiterpene lactone, 13-hydroxy-8,9-dehydroshizukanolide was also identified in the hydroalcoholic extract obtained from stems and leaves of *H. brasiliense* (Trentin et al. 1999, Calixto et al 2001). Other sesquiterpene lactones, 7,10-Epoxy-hedyosminolide or 7α,10α-epoxy-1α(H),5α(H)-guaia-3,11(13)-dien-8α,12-olide were isolated from plant leaves *H. arborescens,* in Guadeloupe, French West Indies (Bercion te al 2006).

Su et al. (2008) isolated for the first time from ethanolic extract of the *H. orientale* aerial parts five guaiane-type sesquiterpenoids, hedyosumins A, B, C, D and E, respectively. Additionally, two sesquiterpenoids compounds 10αR-hydroxy-1,5αRH-guaia-3,7(11)-dien-8αR,12-olide and 9αR-hydroxyasterolide have been isolated for the first time from natural sources. The first one synthesized previously by Blay et al. (2000) from the santonins.
Moreover, two sesquiterpenoid dimers have been recently reported from Fan et al. (2018), Hedyorienoid A and B, respectively (Tolardo et al., 2010).
Finally, two sesterterpenes, bolivianine and isobolivianine, were isolated in ethyl acetate extract from *H. angustifolium* (Acebey et al 2010, 2007): these molecules have been widely investigated in order to develop new organic synthesis models.

4.2 Hydroxycinnamic acid derivatives.

As reported by Amoah et al., (2015), rosmarinic acid and isorinic acid (caffeoyl-4'-hydroxy-phenyllactic acid) have been isolated from fresh leaves of *H. brasiliense* by hot infusion: isorinic acid is considered one of the rosmarinic acid biosynthesis intermediates. The rosmarinic acid is known to possess various biological activities like anticancer, neurochemical, antioxidant (Amoah et al. 2015). Rosmarinic acid has been recently reported as hepatoprotective compound (Lin et al., 2017) and for the prophylaxis and treatment of neuropathic pain (Rahbardar et al., 2018). Moreover, another recent study performed by Cornejo et al., (2017) on rosmarinic acid, showed a promising result concerning the prevention of fibrillization linked to Alzheimer's disease. A previous study from the same authors mentioned also the presence of the other hydroxycinnamic acid derivatives named ethyl caffeate (Amoah et al., 2013).

4.3 Flavonoids

A few reports are available on flavonoids from *Hedyosmum*, and this certainly represents an area for future investigation for both the application and characterization fields. An early report by Cárdenas et al. 1993 describes the isolation of two flavonoid glycosides by n-butanol extracts of the leaves of *H. bonplandianum*, kaempferol 3-*O*-[*α*-L-rhamnopyranosyl(1→6)-*β*-D-glucopyranoside] and kaempferol 3-*O*-[*β*-D-glucopyranoside] respectively. These findings correlate the presence of flavonoids to a folk medicinal use as analgesic in Colombia. Rainer (2013) mentioned antibiotic activity of *H. racemosum* folk medicinal use that probably correlated to the presence of flavonoids.
Recently, Amoah et al. 2015 reported the presence of isolated kaempferol-3-O-β-*D*-glucuronide in *H. brasiliense*. This presence well correlate also with the traditional uses reported (Table 1). It has to be noted that kaempferol is a very important flavonoid as functional food ingredient and for the large range of therapeutic applications such as antioxidant, anti-inflammatory and anti-cancer applications. Its action involves several intracellular and extracellular targets that regulates apoptosis, cell cycle, invasion or metastasis, angiogenesis and inflammation. Further research to confirm its presence in other *Hedyosmum* species is certainly to be encouraged.

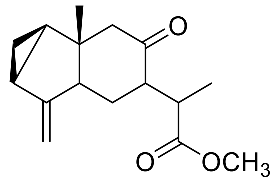
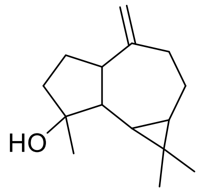
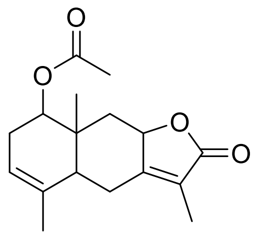
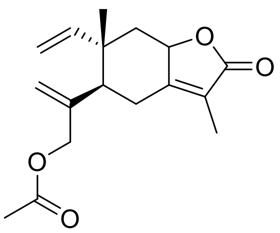
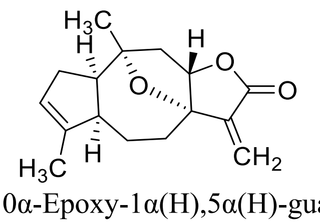
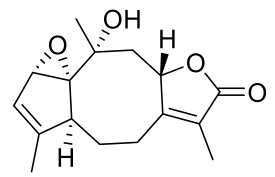
4.4 Neolignans

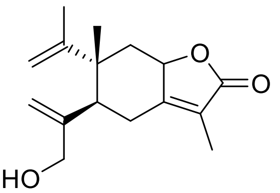
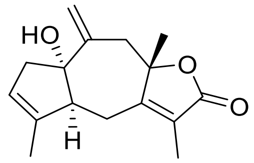
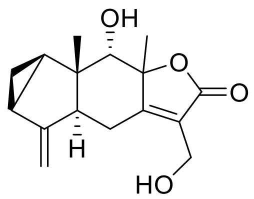
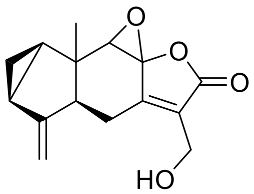
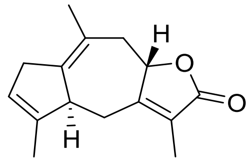
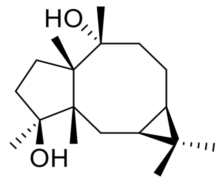
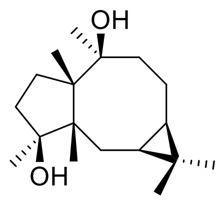
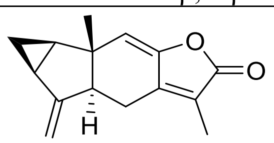
The neolignans prompted to the attention of researchers due to the activity to the most well-known member of this class magnolol and honokiol, wich are the main substances responsible for the beneficial properties of the magnolia bark extract. This interesting class of molecules is still underexploited notwithstanding the initial interest followed by the discovery their potent antiplatelet activity (Shen, 1991). The neolignans (7S, 8R)-5-methoxydihydrodehydrodiconiferyl alcohol-4-O- *β* -D-glucopyranoside and (7S, 8R)-urolignoside have been isolated from the fresh leaves *H. brasiliense* by Amoah et al. (2015). This is the first report of these compounds in the genus *Hedyosmum,* previously they were found in other Chloranthaceae species such as *Chloranthus japonicus* (Kuang et al. 2009) and *Sarcandra glabra* (Wu et al. 2012). Reports on neolignans in *Hedyosmum* are very few thus becoming a suggested topic in this contest.

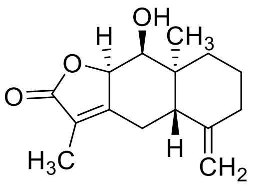
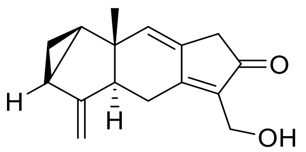
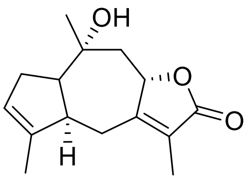
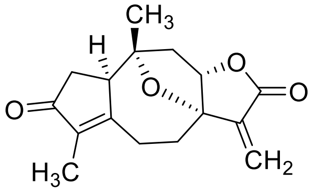
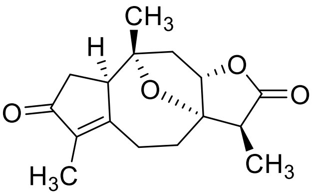
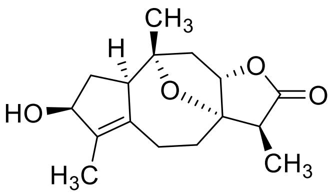
4.5 Other compounds

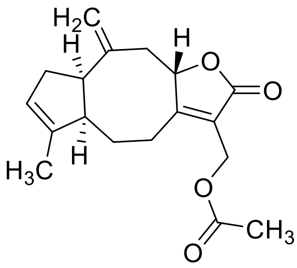
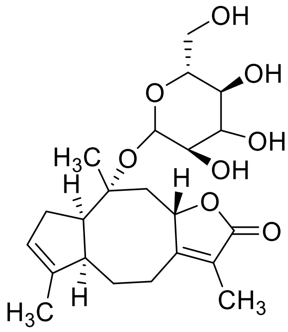
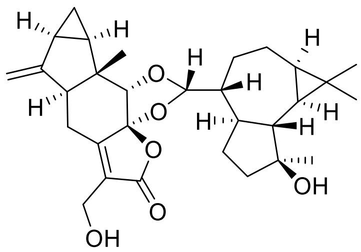
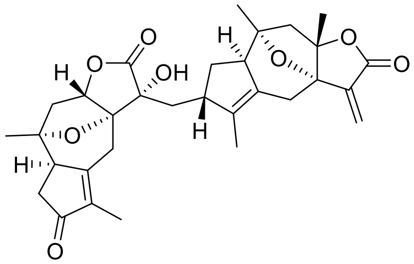
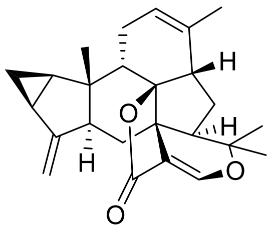
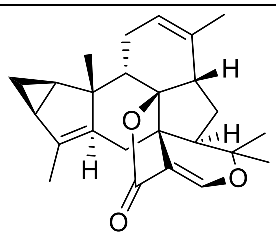
Concerning *H. brasiliense*, several compounds have been detected in hydro-alcoholic double-distillate fractions partitioned with n-hexane and EtOAc solvents (Amoah et al. 2013). The authors obtained phenolic aldehydes: vanillin, protocatechuic aldehyde and 3, 4-Dihydroxybenzaldehyde which represent a precursor in the biosynthesis of vanillin. Another important compound isolated from *H. brasiliense* is vanillic acid. Finally, the coumarin scopoletin has been detected.

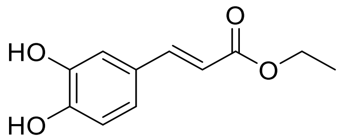
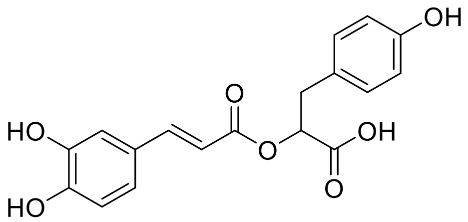
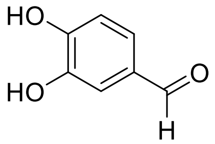
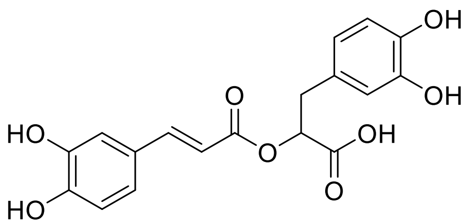
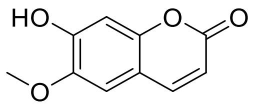
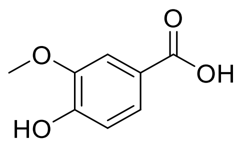
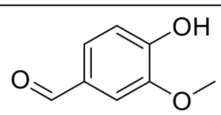
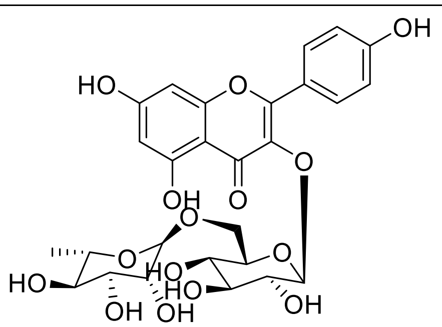
Table 2 - Chemical constituents isolated and characterized from the most in-depth studied species belonging to the genus Hedyosmum (excluding essential oils).

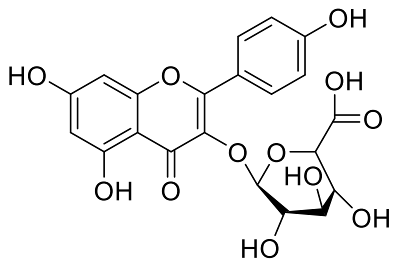
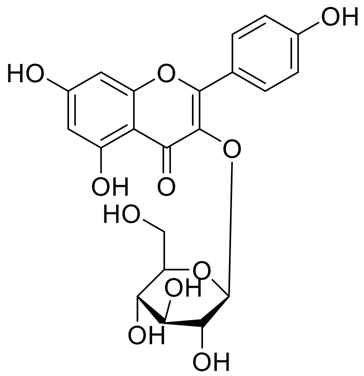
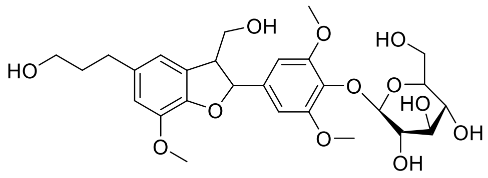
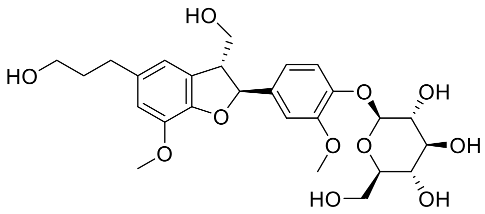
N.	Name and Structure	*Species*	Plant part(s)/solvent(s)	Ref.
1	 Hedyosmone	*H. angustifolium*	Stem bark/ Ethyl acetate	Acebey et al., (2007, 2010)
2	 Spathulenol	*H. angustifolium* *H.Orientale*	Stem bark/ Ethyl acetate Aerial parts/n.r	Acebey et al., (2007, 2010) Zhang et al., (2016)
3	 1-α-acetoxyeudesma-3,7(11)-dien-8,12-olide	*H. brasiliense*	Leaves/ infusion	Amoah et al., 2015b
4	 15-acetoxy-isogermafurenolide	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v)	Amoah et al.,2013
5	 7α,10α-Epoxy-1α(H),5α(H)-guaia-3,11(13)-dien-8α,12-olide	*H. arborescens*	Leaves/Petrol ether Leaves/n.r.	Bercion et al., (2005, 2006) Zhang et al., (2016)
6	 1,2-Epoxy-10α-hydroxy-podoandin	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v) Leaves/n.r.	Amoah et al., (2013) Zhang et al., (2016)

7	 15-hydroxy-isogerma-furenolide	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v) Leaves/ infusion	Amoah et al., (2013 2015b)
8	 1-hydroxy-10(15)-methylenepodoandin	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v) Leaves/n.r.	Amoah et al., (2013) Zhang et al., (2016)
9	 8α/β,9α hydroxyl-onoseriolide	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v)	Amoah et al., (2013)
10	 Oxyonoseriolide	*H. angustifolium*	Stem bark/ Ethyl acetate	Acebey et al., (2007, 2010)
11	 Podoandin	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v) Leaves/ Infusion Leaves/n.r.	Amoah et al., (2013, 2015a, 2015b) Zhang et al., (2016)
12	 Aromadendrane-4β,10α-diol	*H. brasiliense*	Leaves/ Ethanol 95%	Amoah et al., (2015)
13	 Aromadendrane-4β,10β-diol	*H. orientale*	Aerial parts/ Ethanol 95%	Su et al., (2008)
14	 Chloranthalactone A	*H. angustifolium*	Stem bark/ Ethyl acetate	Acebey et al., (2007) Zhang et al., (2016)

15	 9αR-hydroxyasterolide	*H. orientale*	Aerial parts/ Ethanol 95%	Su et al., (2008) Zhang et al., (2016)
16	 13-hydroxy-8,9-dehydroshizukanolide	*H. arborescens* *H. angustifolium* *H. brasiliense* *H. orientale*	Leaves/n.r. Stem bark/ Ethyl acetate Leaves/ EtOH–H_2O (95:5, v/v) Leaves/ Infusion Aerial parts/n.r.	Calixto et al., (2001) Acebey et al., (2007, 2010) Zhang et al., (2016) Amoah et al., (2013, 2015a, 2015b) Zhang et al. (2016) Zhang et al., (2016)
17	 10αR-hydroxy-1,5αH-guaia-3,7(11)-dien-8α,12-olide	*H. orientale*	Aerial parts/ Ethanol 95% Aerial part/n.r	Su et al., (2008) Zhang et al., (2016) .
18	 Hedyosumin A	*H. orientale*	Aerial parts/ Ethanol 95% Aerial parts/n.r.	Su et al., (2008) Zhang et al., (2016)
19	 Hedyosumin B	*H. orientale*	Aerial parts/ Ethanol 95% Aerial parts/n.r.	Su et al., (2008) Zhang et al. (2016)
20	 Hedyosumin C	*H. orientale*	Aerial parts/ Ethanol 95% Aerial parts/n.r.	Su et al., (2008) Zhang et al., (2016)

21	 Hedyosumin D	*H. orientale*	Aerial parts/ Ethanol 95% Aerial parts/n.r.	Su et al., (2008) Zhang et al., (2016)
22	 Hedyosumin E	*H. orientale*	Aerial parts/ Ethanol 95% Aerial parts/n.r.	Su et al., (2008) Zhang et al., (2016)
23	 Hedyorienoid A	*H. orientale*	Twigs and leaves/ Ethanol 95%	Fan et al., (2018)
24	 Hedyorienoid B	*H. orientale*	Twigs and leaves/ Ethanol 95%	Fan et al., (2018)
25	 Bolivianine	*H. angustifolium*	Trunk bark/ Ethyl acetate	Acebey et al., (2010)
26	 Isobolivianine	*H. angustifolium*	Stem bark/ Ethyl acetate	Acebey et al. (2007, 2010)

27	 Ethyl caffeate	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
28	 Isorinic acid	*H. brasiliense*	Leaves/ infusion	Amoah et al. (2015b)
29	 Protocatechuin aldehyde	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
30	 Rosmarinic acid	*H. brasiliense*	Leaves/ infusion	Amoah et al. (2015b)
31	 Scopoletin	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
32	 Vanillic acid	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
33	 Vanillin	*H. brasiliense*	Leaves/ EtOH–H_2O (95:5, v/v)	Amoah et al. (2013)
34	 Kampeferol 3-O-[α-L-rhamnopyranosyl(1→6)-β-D-	*H. bonplandianum*	Leaves/ Petroleum ether	Cárdenas et al. (1993)

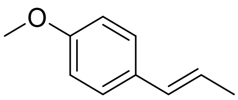
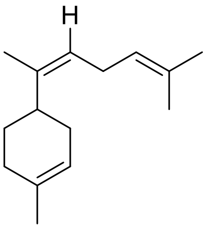
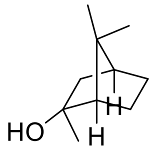
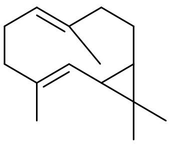
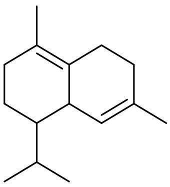
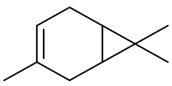
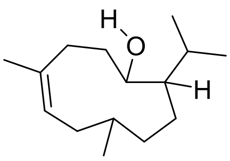
	glucopyranoside]			
35	 Kaempferol 3-O-β-D-glucuronide	*H. brasiliense*	Leaves/ infusion	Amoah et al. (2015b)
36	 Kaempferol 3-O-[β-D-glucopyranoside]	*H. bonplandianum*	Leaves/ Petroleum ether	Cárdenas et al. (1993)
37	 (7S, 8R)-5-methoxydihydrodehydrodiconiferyl alcohol-4-O-β-D-glucopyranoside	*H. brasiliense*	Leaves/ infusion	Amoah et al. (2015b)
38	 (7S, 8R)-urolignoside	*H. brasiliense*	Leaves/ infusion	Amoah et al. (2015b)

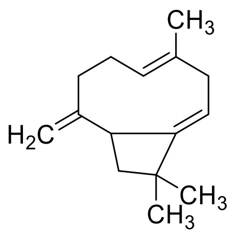
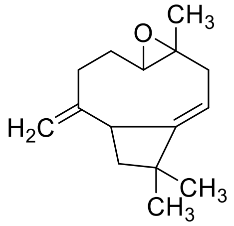
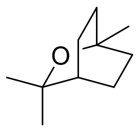
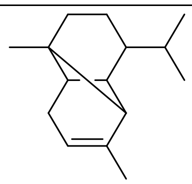
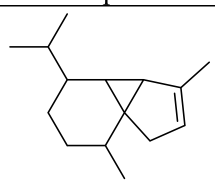
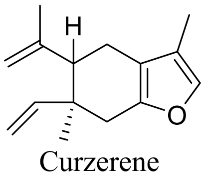
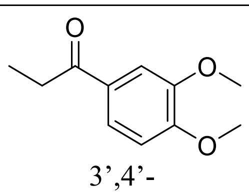
4.6 Essential oils from *Hedyosmum* genus

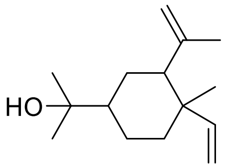
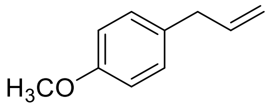
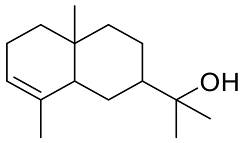
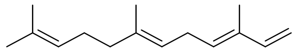
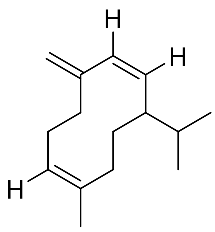
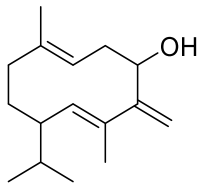
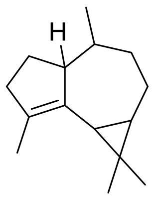
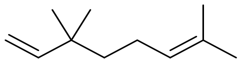
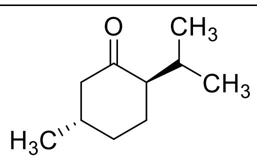
The *Hedyosmum* genus is also a source of essential oils (EOs). Several studies have been performed on different species and different parts of the plant such as: aerial parts, leaves, flowers, and fruits. Terpenes including mainly sesquiterpenoids and monoterpenes are the major constituents of essential oils obtained by this genus. Table 4 summarizes the main compounds of *Hedyosmum* essential oils.

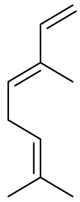
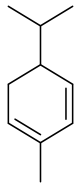
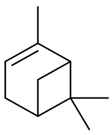
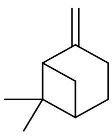
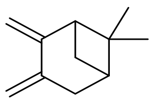
An important amount of data concerning essential oils from *Hedyosmum* genus has been reported (Guerrini et al., 2016; Kirchner et al., 2010, Murakami et al., 2017; Correa-Royero et al., 2010). Two bicyclic monoterpenes, β-Pinene and Sabinene, are the most common constituents of *Hedyosmum* EOs and have been detected in 5 different species, followed by the sesquiterpene Germacrene D (4 species), the isoprenoid Pinocarvone and the cyclic monoterpene α-Phellandrene (3 species). β-Pinene has been reported for its promising antifungal activity against *Candida albicans* and for the synergistic bactericidal effect against methicillin-resistant *Staphylococcus* *aureus*, in combination with ciprofloxacin (Rivas da Silva et al., 2012). A study performed by Zhang et al., 2015 showed a synergistic effect of β-Pinene and Paclitaxel against the non-small-cell lung cancer cells (NSCLC). β-Pinene has been also reported as a component of several essential oils: recent researches focused on Chines traditional medicine mentions its analgesic and anti-inflammatory activities, its effectiveness for the control of *Rhodnius nasutus*, the vector of Chagas disease (de Souza et al., 2018), and its potential as pest control agent against *Tribolium castaneum* (Pajaro-Castro et al., 2017). Also Sabinene, Germacrene D and other main components of the *Hedyosmum* EOs have been extensively reported in several other studies concerning essential oils.

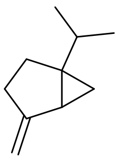
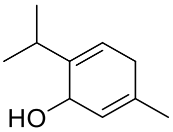
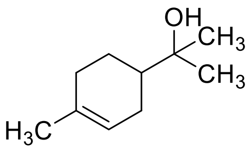
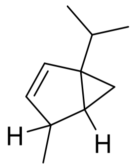
Table 3 – Main chemical components identified and characterized in the essential oils obtained by the most in-depth studied species belonging to the genus Hedyosmum.

N.	Name and Structure	Species	Amount % (w/w)	Plant part	Ref.
39	 Anethole	*H. scabrum*	6.6%	Leaves	De Feo and Soria (2007)
40	 α-Bisabolene	*H. bonplandianum*	10.3%	Leaves	Mundina et al. (2000)
41	 Borneol	*H. glabratum*	6.8%	Leaves	Danis et al. (2012)
42	 Bicyclogermacrene	*H. arborescens*	10.6%	Leaves	Sylvestre et al. (2007)
43	 δ-Cadinene	*H. sprucei*	5.5%	Fresh aerial part	Guerrini et al. (2016)
44	 δ-3-Carene	*H. scabrum*	12.1%	Aerial part	Lorenzo et al. (2006)
45	 Carotol	*H. brasiliense*	9.8% 9.4% 6.5% 5.9%	Female flowers Male flowers Female leaves Male leaves	Murakami et al. (2017)

46	 β-Caryophyllene	*H. costaricensis* *H. translucidum*	6.1% 7.8%	Leaves Leaves	Mundina et al. (2000), Zamora-Burbano and Arturo-Perdomo (2016)
		H. sprucei	15.5%	Fresh aerial part	Guerrini et al. (2016)
47	 Caryophyllene oxide	*H. translucidum*	5.3%	Leaves	Zamora-Burbano and Arturo-Perdomo (2016)
48	 1,8-Cineole	*H. angustifolium*	3.7%	Aerial parts	Lorenzo et al. (2006)
		H. brasiliense	6.9%	Leaves from male plant	Murakami et al. (2017)
			4.6%	Leaves from female plant	
			7.2%	Leaves from male flowers	
		H. scabrum	10.8%	Leaves from male plant	Herrera et al. (2018)
			20.5%	Leaves from female plant	
49	 α-Copaene	*H. glabratum* *H. sprucei*	8.6% 5.1%	Leaves Fresh aerial part	Danis et al. (2012) Guerrini et al. (2016)
50	 α-Cubebene	*H. glabratum*	9.5%	Leaves	Danis et al. (2012)
51	 Curzerene	*H. brasiliense*	8.9%	Leaves	Kirchner et al. (2010)
52	 3',4'-Dimethoxypropiophenone	*H. scabrum*	6.6%	Aerial part	Lorenzo et al. (2006)

53	 Elemol	*H. traslucidum*	5.8%	Leaves	Zamora-Burbano and Arturo-Perdomo (2016)
54	 Estragole	*H. scabrum*	55.8%	Leaves	De Feo and Soria (2007)
55	 α-Eudesmol	*H. translucidum*	11.4%	Leaves	Zamora-Burbano and Arturo-Perdomo (2016)
56	 (E,E)-α-Farnesene	*H. costaricence*	32.0%	Leaves	Mundina et al. (2000)
57	 Germacrene-D	*H. scabrum*	13.0%	Aerial parts	Lorenzo et al. (2006)
		H. sprucei	23.2%	Fresh aerial part Leaves	Guerrini et al. (2016)
		H. translucidum	8.9%	Leaves	Zamora-Burbano and Arturo-Perdomo (2016)
		H. costaricence	32.0%		Mundina et al. (2000)
58	 D-germacren-4-ol	*H. scabrum*	12.6%	Leaves from male plant	Herrera et al. (2018)
59	 α-Gurjunene	*H. scabrum*	6.6%	Aerial part	Lorenzo et al. (2006)
60	 Linalol	*H. angustifolium* *H. scabrum*	6.1% 16.5%	Aerial parts Leaves from female plant	Lorenzo et al. (2006) Herrera et al. (2018)
61	 *trans*-menthone	*H. mexicanum*	3.0%	Leaves	Mundina et al. (2000)

62	 (E)-β-Ocimene	*H. bomplandianum*	10.8%	Leaves	Mundina et al. (2000)
63	 α-Phellandrene	*H. arborescens*	11.4%	Leaves	Sylvestre et al. (2007)
		H. brasiliense	8.1%	Leaves from female flowers	Murakami et al. (2017)
		H. sprucei	3.5%	Fresh aerial parts	Guerrini et al. (2016)
64	 α-Pinene	*H. angustifolium*	24.0%	Aerial parts	Lorenzo et al. (2006)
		H. scabrum	7.7%	Leaves	De Feo and Soria (2007)
		H. scabrum	6.4%	Leaves from male plant	Herrera et al. (2018)
		H. scabrum	15.0%	Leaves from female plant	Herrera et al. (2018)
65	 β-Pinene	*H. angustifolium*	23.5%	Aerial parts	Lorenzo et al. (2006)
		H. brasiliense	5.2%	Leaves from male plant	Murakami et al. (2017)
		H. colombianum	11.4–16.5%	Leaves	Delgado et al. (2010)
		H. mexicanum	4.6%	Leaves	Mundina et al. (2000)
			8.0%	Fruits	Mundina et al. (2000)
		H. scabrum	4.8%	Leaves from male plant	Herrera et al. (2018)
			6.4%	Leaves from female plant	
66	 Pinocarvone	*H. brasiliense*	4.5%	Leaves from female plant	Murakami et al. (2017)
			3.2%	Leaves from male flowers	
			3.7%	Leaves from female flowers	
			8.4%	Leaves	Kirchner et al. (2010)
		H. colombianum	13.4%	Leaves	Delgado et al. (2010)
		H. scabrum	14.2% 13.1%	Leaves from male plant	Herrera et al. (2018)

67	 Sabinene	*H. arborescens*	9.7%	Leaves	Sylvestre et al. (2007)
		H. bomplandianum	14.7%	Leaves	Mundina et al. (2000)
		H. brasiliense	15.8%	Leaves from male plants	Murakami et al. (2017)
			15.8%	Leaves from female plants	
			8.5%	Leaves from male flowers	
			9.5%	Leaves from female flowers	
		H. mexicanum	24.0%	Leaves	Mundina et al. (2000)
			24.6%	Fruits	
		H. scabrum	6.3%	Leaves from female plant	Herrera et al. (2018)
68	 Terpinen-3-ol	*H. bomplandianum*	7.0%	Leaves	Mundina et al. (2000)
		H. mexicanum		Fruits	Mundina et al. (2000)
69	 α-Terpineol	*H. brasiliense*	10.2%	Leaves	Kirchner et al. (2010)
68	 β-Thujene	*H. brasiliense*	7.1%	Leaves	Kirchner et al. (2010)

4.7 Other related topics regarding the *Hedyosmum* genus phytochemistry

As for the studies reported, one of the principal findings regards the natural active compounds obtained by species belonging to the *Hedyosmum* genus, especially bolivianine, isobolivianine and onoseriolide. They have been used as starting points for innovative researches in bioinspired synthesis procedures (Yuan et al., 2013; Du et al., 2014; Ardkhean et al., 2016; Fan et al. 2016; Sun et al. 2016; Hugelshofer and Magauer 2017; Li et al., 2017). The bioinspired approach plays a key role in discovery and constantly opens innovative perspectives in the study of new active compounds. It should be noted that sesterterpenes are unusual compounds, often present in various marine organisms, especially sponges, but also obtained from bacteria and plants. Sesterterpenes have been extensively studied for their peculiar chemical structures and for the anticancer and the cytotoxic activity (Kaweetripob, 2018; Evidente, 2016; Wang, 2012; Ebada, 2010).

5. Pharmacological effects

Ethnomedical practices and traditional uses of plants are very often source of inspiration and useful starting points for studies regarding various types of biological activities. This is the case of *Hedyosmum* genus, whose ethnomedical reports have been used as a guide for many biological investigations. In this section several different biological activities of the various *Hedyosmum* species are listed and briefly described related to essential oils, various types of extracts and isolated compounds belonging to *Hedyosmum* species. Pharmacological effects have been summarized in Tables 4 and 5.

5.1 Neuroprotective, anxiolytic, antidepressant and sedative effects

Isolated compounds from *H. brasiliense* have been investigated *in vivo* as neuroprotective agents. Precisely, ARD (aromadendrane-4β,10α-diol), 13HDS (13-hydroxy-8,9-dehydroshizukanolide) and PDA (Podoandin) significantly enhanced the Aβ1-42 peptide- induced memory impairment in the passive avoidance test, without increasing adverse effects on locomotor activities (Amoah et al., 2015a).
As reported by Tolardo et al. (2010), *H. brasiliense* ethanolic extract and an isolated compound, podoandin, were studied and a preliminary neuropharmacological screening revealed anxiolytic, antidepressant, sedative and hypnotic activities that correspond to the ethnobotanical information.
A research performed by Gonçalves et al. (2012) demonstrated that *H. brasiliense* crude extract and PDA can induce an antidepressant-like effect on mice (Forced swimming test - FST). In the same study, the mice were pretreated with selective receptor antagonists in order to investigate the possible involvement of dopaminergic, GABAergic, noradrenergic, opioid, oxidonitrergic and serotonergic systems and to better understand the biological mechanism of the antidepressant-like activity. The results seem to involve dopaminergic, noradrenergic and serotonergic systems, but not on the GABAergic, oxidonitrergic and opioid systems.

5.2 Analgesic and antinoniceptive effect

Cárdenas et al. (1993) carried out a research on *H. bonplandianum* n-butanol extract and two flavonoid glycosides extracted from the leaves, Kaempferol 3-*O*-[*α*-L-rhamnopyranosyl(1→6)-*β*-D-glucopyranoside] and Kaempferol 3-*O*-[*β*-D-glucopyranoside] respectively. A preliminary *in vivo* study on mice exhibited a significant analgesic activity, according to ethnobotanical reports of Colombian folk medicine practices. A previous test performed by Di Stasi et al. (1988) on the same species showed the analgesic activity *in vivo* (writhing test) of the aqueous ethanol (50:50, v/v) extract, which was concentrated to allow the administration of 1 g/kg doses in mice.
In a study regarding the hydroalcoholic extracts of *H. brasiliense* stems and leaves, Trentin et al. (1999) proved for the first time a dose-related antinociception effect in different types of chemical pain in mice. Also the sesquiterpene lactone 13-hydroxy-8,9-dehydroshizukanolide (13HDS), isolated from the same species, showed antinociceptive activity. A further work by Martini et al. (2007) regards the antinociceptive effects of several compounds belonging to plants reported as useful in Brazilian folk medicine. The sesquiterpene 13HDS, isolated from leaves and stems of *H.brasiliense*, was able to inhibit the [^{3}H] glutamate binding and the [^{3}H] glutamate uptake by synaptic vesicles *in vitro*.

5.3 Anti-erectile dysfunction effect

A research performed by Leitolis et al. (2016) on *H. brasiliense* investigated the relaxant effects of two isolated compounds, 13-hydroxy-8,9-dehydroshizukanolide (podoandin) and 15-acetoxy-isogermafurenolide (elemanolide) and of the hexane fraction obtained from ethanol leaves extract, on endothelium-intact and endothelium-denuded rat aortic rings and strips of *corpus cavernosum*. The results of the study support the aphrodisiac effect of *H. brasiliense* reported by ethnobotanical information (Reitz et al. 1965). These findings may open a new research path regarding erectile dysfunction. The authors suggest that further studies involving cardiovascular diseases are needed, despite the absence of ethnobotanical information.

5.4 Anticancer effect

In Acebey et al., (2010) it is reported the cytotoxic effect of five sesquiterpenes isolated from the ethyl acetate extracts of the bark of *H. angustifolium*, respectively named: oxyonoseriolide, hedyosmone, onoseriolide, chloranthalactone A and spathulenol. Cytotoxic assay was performed *in vitro* on human breast cancer cells (MCF-7) and human leukemia monocyte cell line (THP-1). Oxyonoseriolide displayed strong cytotoxicity against VERO cells but moderate cytotoxicity against MCF-7 and THP-1 cells (IC_{50} values 0.2 μM, 23.8 μM and 4.2 μM, respectively).
As reported by Sylvestre et al. (2007) the essential oil obtained from leaves of *H. arborescens* was tested in order to determine the cytotoxic activity against human lung carcinoma (A-549) and human colon adenocarcinoma (DLD-1) cell lines. The oils were able to express a moderate anticancer activity against both cell lines, with a GI_{50} (concentration of the EO which allow inhibiting the 50% of cell line's growth) value of 178±9 μg/ml for DLD-1 and 158±7 μg/ml for A-549.

H. orientale has been investigated by Su et al. (2008) in order to identify the cytotoxic activity of the ten isolated guaiane-type sesquiterpenoids. All compounds were evaluated for their cytotoxic activities against human lung adenocarcinoma (A-549) and human leukemia (HL-60) tumor cell lines. Only one of the above mentioned molecules, 9α-hydroxyasterolide, exhibited moderate activities against both A-549 and HL-60 cell line (IC_{50} values 3.1 μM and 8.8 μM respectively). Fan et al., (2018) reported for the first time the presence of two sesquiterpenoid dimers, Hedyorienoid A and B: the second one showed a promising NF-κB inhibitory activity. Additionally, *H. sprucei* essential oil showed a remarkable cytotoxic activity against MCF-7 (IC_{50} values 32.76 ± 4.92 μg/mL and 33.64 ± 0.43 μg/mL at 48h and 72h respectively) and A549 (IC_{50} values 44.05 ± 2.35 μg/mL and 43.55 ± 2.80 μg/mL at 48h and 72h respectively) cell lines (Guerrini et al., 2016).

5.5 Anti-bacterial and anti-plasmodial effect

The essential oil of *H. brasiliense* was studied in order to investigate its *in vitro* inhibitory effects against six bacterial species (*Bacillus subtilis, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus* and *Staphylococcus saprophyticus*) and six fungal species (*Candida albicans, Candida parapsilosis, Microsporum canis, Microsporum gypseum, Trichophyton rubrum* and *Trichophyton mentagrophytes*). The oil showed low activity against Gram-negative strains but was able to express a good antibacterial activity (MIC values from 0,125 to 2,5 % v/v) against the Gram-positive bacteria and human opportunistic pathogenic fungi and dermatophytes (Kirchner et al. 2010).
Another study regarding sesquiterpenoids obtained from *H. brasiliense* was carried out by Amoah et al. (2013), the work starts with the isolation of seven compounds (1,2-epoxy-10a-hydroxy-podoandin, 1-hydroxy-10,15-methylenepodoandin, 15-acetoxy-isogermafurenolide, 8α/β,9αhydroxy-onoseriolide, podoandin, onoseriolide , 15-hydroxy-isogermafurenolide) which have been tested against isoniazid-sensitive *Mycobacterium tuberculosis* cultures. None of these sesquiterpene lactones showed anti-mycobacterial activity at concentrations ranging from 1 to 30 μM.
A research performed on infusions obtained by fresh leaves of female and male plants of *H. brasiliense* (Amoah et al. 2015a), focused on the antimicrobial activity of the infusion and its main components (rosmarinic acid, isorinic acid, (7S, 8R)-5-methoxydihydrodehydrodiconiferyl alcohol-4-O-b-D-glucopyranoside, (7S, 8R)-urolignoside, podoandin, onoseriolide, 1-a-acetoxyeudesma-3,7(11)–dien–8,12–olide, 15-hydroxy-isogerma-furenolide, kaempferol-3-O-β-*D*-glucuronide) against *Mycobacterium tuberculosis.* No significant activity was evidenced at concentrations ranging from 100 μg/mL to 1.56 μg/mL.
Murakami et al. 2017 performed a research regarding the chemical composition, the antifungal and the antioxidant activities of *H. brasiliense* essential oil. Four oils were obtained by hydrodistillation, from leaves and flowers of both male and female trees. Female flowers essential oil showed consistent antifungal activity against *Cladosporium sphaerospermum* Penz and *Cladosporium cladosporioides*. The other essential oils showed weakest activities. In 2010, a research performed by Acebey et al. concerned the anti-leishmanial activity, the cytotoxic effect and the antiplasmodial activity of five sesquiterpenos isolated from the ethyl acetate extracts of the bark of *H. angustifolium*, respectively named: oxyonoseriolide, hedyosmone, onoseriolide, chloranthalactone A and spathulenol. Onoseriolide resulted the main active compound against two axenically cultured amastigotes, *Leishmania amazonensis* (IC_{50} 19.8 μM) and *Leishmania infantum* (IC_{50} 20.9 μM). Also intramacrophagic amastigotes were tested and the assay showed IC_{50} values between 24.3μM and 29.1 μM. Onoseriolide exhibited also moderate antiplasmodial activity and weak cytotoxicity.

5.6 Other bio-effects

H. bonplandianum ethanolic extract from leaves has been investigated by radioligand-binding techniques, in order to study the inhibition of the [3H] BQ-123 binding (endothelin-1 ETA receptor). The assay represents a preclinical model for the treatment of cardiovascular, mental and feeding disorders and hypertension. In this *in vitro* model bioactive compounds binds to G-protein coupled receptor subtypes which seems to be involved in the diseases mentioned above. In a preliminary screening, the extract showed a high inhibitory activity, opening new research opportunities in the field of endothelin receptor antagonists.
Correa-Royero et al. (2010) have evaluated antifungal activity and cytotoxic effect on VERO cell line of 32 essential oils. From this *in vitro* study emerged that, according to the American National Cancer Institute (USA) criteria of cytotoxic activity for the crude extracts established in an IC_{50}<30 μg/mL, the essential oils of

Hedyosmum spp. (*scaberrium* and *racemosum*) were cytotoxic oils. This data are very important in order to find antifungal compounds with a low-toxic profile.
Hedyorienoid B, a sesquiterpenoid dimer obtained from *H. orientale*, has been tested in order to check its inhibitory activity of NF-κB, a key factor involved in anti-inflammatory process, cell survival and apoptosis and metabolic diseases: the mentioned compound 12 showed promising NF-κB inhibitory activities with IC_{50} value of 5.34 ± 2.21 μM. (Fan et al., 2018).
Murakami et al. (2017) have investigated for the first time the antioxidant activity of *H. brasiliense*. In this study they have investigated the chemical composition of the essential oils from *H. brasiliense* male and female flowers and leaves collected at Ilha do Cardoso (São Paulo, Brazil) and compared their antioxidant activity by DPPH and β-carotene/linoleic acid assays. *H. brasiliense* essential oils proved to be much more active in the β-carotene bleaching test with IC_{50} values from 71.12 to 180.71 mg/mL demonstrating their ability to destroy the conjugated diene hydroperoxides.
Guerrini et al. (2016) have evidenced an interesting profile in terms of antioxidant activity of *H. sprucei* essential oil: they reported an IC_{50} value of 230 ± 10 *μ*g/mL regarding DPPH scavenging activity, about 30% better than standard positive control used (Thymol, IC_{50} = 318 ± 7 *μ*g/mL).

Table 4 – The main relevant reported biological activities of pure compounds in *Hedyosmum* species (excluding essential oils and crude extracts).

No. of compound	Model		Reported biological activities	Positive control	Negative control	Ref.
4	*In vivo*		Relaxant effects on endothelium-intact and endothelium-denuded rat aortic rings and strips of *corpus cavernosum*, 51.1 ± 11.6%, 26.0 ± 5.1%, 57.9 ± 5.5%, respectively (DRD: 10 nM to100 µM;)	NA	Vehicle	Leitolis et al. (2016)
12	*In vivo*		Amyloid-β peptide-induced Alzheimer's disease mouse model (DRD: 400pmol/mouse, checked after 7 days, with1 mg/site of 3, MAC: NA)	NA	NA	Amoah et al. (2015a)
23	*In vitro*		NF-κB inhibitory activity with IC_{50} values of 5.34 ± 2.21 µM (DRD: 6 doses at a dilution ratio of 1:3, followed by stimulation with 10 ng/ml TNF-α, 6 h, MAC: NA; IC_{50} = 0.037 µM)	PS-341	NA	Fan et al. (2018)
15	*In vitro*	1.	Cytotoxicity against A-549 cell *in vitro*, IC_{50} = 3.1 *µ*M (; 0 of)	Pseudolaric acid B (0.30 *µ*M ag IC_{50} aginst A-549)	NA	Su et al. (2008)
		2.	Cytotoxicity against HL-60 cell *in vitro*, IC_{50}= 8.8 *µ*M 50	Etoposide (0.20 µM against HL-60)	NA	
16	*In vivo*	1.	Amyloid-β peptide-induced Alzheimer's disease mouse model (DRD: 400 pmol/mouse, checked after 7 days, with1 mg/site of 17, MAC:NA)	NA	NA	Amoah et al. (2015a)
	In vitro	2.	Anti-leishmanial activities, IC_{50} 19.8 µM against *L. amazonensis*	Amphotericin B	NA	Acebey et al. (2010)
	In vitro	3.	Anti-leishmanial activities, IC_{50} 20.9 µM against *L. infantum*	Pentamidine	NA	
	In vitro	4.	Anti-leishmanial activities, IC_{50} between 24.3 µM and 29.1 µM against intramacrophagic form (*L. infantum*) (DRD: 24 h to 96 h)	Amphotericin B, Pentamidine	NA	

	In vivo	5.	Relaxant effects on endothelium-intact and endothelium-denuded rat aortic rings and strips of *corpus cavernosum*, 90.1 ± 5.9%, 54.6 ± 5.9%, 49.5 ± 3.9%, respectively (DRD: 10 nM to100 µM;)	NA	Vehicle	Trentin et al. (1999)
	In vivo	6.	Antinociception against acetic-acid writhing, 89±2, 57 ±4 and 52 ±5% according to i.p., i.c.v., and i.t. routes, respectively, in vivo (DRD: intraperitoneally (3±60 mg/kg), intracerebroventricularly or intrathecally (10±100 mg/site) 30, 10, and 10min before acetic acid injection, respectively)	NA	Vehicle i.p. (10 ml/kg), i.c.v. (5 ml/site), or i.t. (5 ml/site)	
	In vivo	7.	Antinociception against capsaicin-induced licking. 60±5, 94 ±4,and 61±5% when the compound was given i.p., i.c.v., or i.t., respectively (DRD: 3±300 mg/kg, i.p.; 1±100mg/i.c.v., or 10±100 mg/i.t; 30, 10, and 10 min before acetic acid injection, respectively).	NA	Appropriate vehicle intraperitoneally (10 ml/kg), i.c.v. (5 ml/site), or i.t. (5 ml/site), 30, 10, and 10 min before capsaicin injection, respectively	
34	*In vivo*		Analgesic activities (Whriting Test), (DRD: 80 and 40 mg/Kg in water MAC: NA)	5 mg/Kg morphine, 75 mg/Kg diklofenac	Water	Cárdenas et al. (1993)
36	*In vivo*		Analgesic activities in vivo (Whriting Test), (DRD: 80 and 40 mg/Kg in water MAC: NA)	5 mg/Kg morphine, 75 mg/Kg diklofenac	Water	Cárdenas et al. (1993)
10	*In vitro*	1.	Cytotoxicity against THP-1 cells, IC_{50} 4.2 µM	NA	NA	Acebey et al. (2010)
		2.	Cytotoxicity against MCF-7 cells, IC_{50} 23.8 µM	NA	NA	
11	*In vivo*	1.	Amyloid-β peptide-induced Alzheimer's disease mouse model (DRD: 400 pmol/mouse, checked after 7 days, with1 mg/site of 30, MAC: NA)	NA	NA	Amoah et al (2015a),
	In vivo	2.	Relaxant effects on endothelium-intact and endothelium-denuded rat aortic rings and strips of *corpus cavernosum*, 86.8 ± 8.0%, 46.6 ± 5.7%, 65.9 ± 7.3%, respectively (DRD: 10 nM to100 µM)	NA	Vehicle	Leitolis et al. (2016)

In vivo	3.	Antidepressant effect, significant reduction in immobility timedecreasing to 51.67%, compared with the controls, *in vitro* (DRD: 10 mg/kg;)	Imipramine (50 mg/Kg)	NA	Tolardo et al. (2010)

DRD, Dose range tested and duration; MAC, Minimal active concentration; NC, Negative control; PC, Positive control; NA, Not available.

Table 5 – The main relevant biological activities of EOs obtained from *Hedyosmum* species.

EOs*	Reported biological activities	Positive control	Negative control	Ref.
H. arborescens	1. Cytotoxicity against DLD-1 (colon adenocarcinoma) cells, IC_{50} 178 ±9 μg/mL (DRD: increasing concentration of EO for 48h)	NA	NA	Sylvestre et al., (2007)
	2. Cytotoxicity against A549 (human lung cancer) cells *in vitro*, IC_{50} 158 ±7 μg/mL (DRD: increasing concentration of EO for 48h)	NA	NA	
H. brasiliense	1. Antioxidant effect by β-carotene/linoleic acid bioassay,, IC_{50} from 80 to 180 μg/mL)	BHY and BHA (IC_{50} of BHT and BHA, 0.08 ± 0.09 μg/mL and 0.27 ±0.02 μg/mL, respectively)	Methanol	Murakami et al., (2017)
	2. Antioxidant effect by DPPH scavenging assay, IC_{50} from 2516.18 to 3783.49 μg/mL	Quercetin and *Ginkgo biloba* (PC: IC_{50} of Quercetin and *Ginkgo biloba* extract, 2.5 ± 0.09 μg/mL and 13.5 ±0.5 μg/mL, respectively)	Methanol	
	3. Activity against human pathogen Gram-positive bacteria *Staphylococcus aureus*, *Staphylococcus saprophyticus* and *Bacillus. subtilis*, (agar dilution method) (DRD: from 2.5 to 0.078 % (v/v), at 35 °C for 24 h, respectively, MAC: both 0.312% (vol/vol))	Vancomycin	Vehicle	Kirchner et al., (2010)
H. sprucey	1. Antioxidant effect by Quantitative Spectrophotometric DPPH scavenging assay, IC_{50} 230 μg/mL)	Thymol (IC_{50} of thymol 318 μg/mL)	Blank DPPH solution	Guerrini et al., (2016)
	2. Activity against human pathogen bacteria, *Listeria grayi* (microdilution method) (DRD: 0.03 μL/mL to 2 μL/mL, at 37 °C for 6h and at 26°C for 24 h, respectively, MAC: 250 μg/mL)	Thymol	Sterile medium	
	3. Activity against human pathogen bacteria *Staphylococcus aureus* (microdilution method) (DRD: 0.03 μL/mL to 2 μL/mL, at 37 °C for 6h and at 26°C for 24 h, respectively, MAC: 1000 μg/mL)	Thymol	Sterile medium	

4. Activity against phytopathogen bacteria, *Clavibacter michiganensis* subsp. *nebraskensis* DSM 20400 (microdilution method*)* (DRD: 0.03 μL/mL to 2 μL/mL, at 37 °C for 6h and at 26°C for 24 h, respectively, MAC: 62μg/mL)	Thymol	Sterile medium
5. Cytotoxicity against MCF-7 (breast adenocarcinoma) cells, IC_{50} 32.76 ± 4.92 and 33.64 ± 0.43 μg/mL after 48 and 72 h, respectively (DRD: 1 to 100 μg/mL for 24, 48, and 72h)	NA	Vehicle
6. Cytotoxicity against A549 (human lung cancer) cells *in*, IC_{50} 44.05 ±2.35 and 43.55 ± 2.80 μg/mL after 48 and 72 h, respectively (DRD: 1 to 100 μg/mL for 24, 48, and 72h)	NA	Vehicle

DRD, Dose range tested and duration; MAC, Minimal active concentration; NC, Negative control; PC, Positive control; NA, Not available.
* All the data concerning the bioactivity of EOs has been performed due to *in vitro* test

5.7 Critical assessments of the papers reviewed

A critical assessment of the papers reviewed has been performed and some conceptual and methodological problems have been identified, especially regarding materials and methods and the experimental design. The assessments was based on the recent guidelines for manuscript submission in the peer-reviewed pharmacological literature (Editorial / Biochemical Pharmacology, 2015; Mullane and Williams, 2015).

For instance, none of the reviewed studies reported if the investigator responsible for data analysis was blinded to which samples or animals represent control and treatment groups. None of the *in vitro* studies mentioned the passage number and population doubling time (PDL) of the used cell lines. Concerning the test on animal model, only 3 reviewed paper mentioned complete data regarding the compliance with regulations on the ethical treatment of animals, including also the which institutional committee or organization approved the experiments design. Only one article reported data concerning the method of anesthesia. Data on sex, weight, age and group size have been adequately reported in 2 papers.

Concerning the main relevant pharmacological data and the quantified results of concentration and dose-response related experiments (such as IC_{50} and/or EC_{50} values, dose range tested, the minimal active concentration, *in vitro* or *in vivo* study, positive and negative control, duration, type of extract) a detailed description is available in Table 4 and 5.

The threshold for statistical significance (P value) was clearly indicated and data were reported as the mean ± standard deviation (SD) of three or more independent experimental replications.

Regarding the reported antioxidant activity on EOs and extracts, the review papers includes different *in vitro* assays such as DPPH test and β-carotene bleaching test, ORAC, FRAP, etc. The antioxidant activity is a wide spread test in phytochemistry studies also for *Hedyosmum* genus, but this kind of test have been partially questioned for their not reliable results in clinical approaches because there is poor evidence that *in vitro* antioxidant activities can be extended to have human studies (Mimica-Dukić et al., 2016, HerbalEGram, 2018),

In addition to the evaluation based on the guidelines for manuscript submission in the peer-reviewed pharmacological literature, all the review papers have been further analyzed concerning the following criteria in order to assess the quality and the validity of the papers reviewed: (a) Is the study linked to the described local and traditional uses?; (b) Is the local and traditional uses adequately described by peer review references? (c) Botanical identification by experts is mentioned; (d) Is the study based on isolated compounds?.

Only 7 of the papers reviewed completely described the relation between the study and the local and traditional use or knowledge, adding also a solid methodology concerning the botanical identification. In all the review papers traditional uses and ethnomedical information are poorly investigated or just partially reported. Moreover, especially in the oldest studies or in the searches performed on essential oils, pharmacological studies was performed only on crude extracts or fractions.

All the above mentioned data evidence some gaps related to conceptual and methodological approaches, especially regarding the material and methods sections of the reviewed papers. Further investigations on isolated compounds should be recommended.

6. Conclusion

The *Hedyosmum* genus has been investigated from several scientists and some promising findings has been found, nevertheless further specific research are needed. The *Hedyosmum* genus seems to be an interesting paradigm of the research path that drives the scale up of the use of plant species from ethnomedical tradition to possible application in modern health products. Despite many plants of the genus *Hedyosmum* have been reported for their traditional uses, including the treatment of depression, pain, migraine, stomach and ovary diseases in Latin America, they are not mentioned into the pharmacopoeia of these countries and research activity is quite poor or incomplete. *H. brasiliense* is the most investigated plant and some traditional uses reported for this species have been partially confirmed by *in vitro* and *in vivo* studies, even if solid clinical evidences are far to be obtained. However, the traditional uses of preparations derived from *Hedyosmum* plants do not evidence relevant toxicological implications, supporting the fact that they could be similarly considered generally recognized as safe as other medicinal plants currently used in modern health products. In particular, *H. orientale* and *H. sprucei* had produced promising preliminary studies, with particular relevance to those conducted by Martini et al., (2007), Tolardo et al., (2010), Gonçalves et al., (2012), Leitolis et al. (2016) about antidepressant activity and erectile dysfunction, even if they seems to deserve further deepening. This framework strengthens the importance to match ethnobotanical and pharmacological researches, in order to exploit the results obtained for bioactivities related to human diseases for further and modern applications.

Although 21 *Hedyosmum* species are mentioned for traditional uses, 16 species (*H. angustifolium*, *H. anisodorum*, *H. arborescens*, *H. bonplandianum*, *H. brasiliense*, *H. crenatum*, *H. cuatrecazanum*, *H. cumbalense, H. goudotianum*, *H. luteynii*, *H. maximum*, *H. nutans*, *H. racemosum*, *H. scabrum*, *H. sprucei*, *H. uniflorum*) of the genus Hedyosmum have been mentioned as traditional remedy and a wide number of ethnomedicinal uses has been reported, including the treatment of pain, depression, migraine, stomach and ovary diseases. 5 species (*H. colombianum*, *H. mexicanum*, *H. purpurascens*, *H. scaberrimum, H. translucidum*) have been reported for their use as flavoring agent, tea substitute, infusion or food. A deepened ethnopharmacology study is needed in order to better recollect and systematize the traditional knowledge concerning the *Hedyosmum* species, also pharmacokinetic and pharmacodynamics studies on the extracts and isolated compounds are strongly recommended. Only one synergistic effect between a *Hedyosmum* species and another plant has been reported as ethnomedical information. Grandtner and Chevrette (2014) mentioned the infusion of *Stenostomum lucidum* and *H. nutans* leaves for the treatment of colic. Unfortunately, no other papers support these information and no data are available concerning the phytochemistry of *Stenostomum lucidum*. Concerning the interaction with prescribed medication, no data have been reported for *Hedyosmum* genus. The preliminary findings described by Martini et al (2007) allow presuming possible interaction of 13HDS (16) with other drugs which interact with the glutamatergic system.

Actually, as reported in the present review, the link between ethnobotanical and pharmacological studies passing through phytochemistry of *Hedyosmum* species seems to be at the beginning of the story thus promising interesting implications.

With specific reference to phytochemical evidences and applications, *Hedyosmum* species derivatives, bolivianine, isobolivianine and onoseriolide are emerging as suggestive starting points for bioinspired synthetic procedures and products. In light of these evidences, further research should be oriented to the development of new molecules by semisynthesis or partial chemical synthesis in order to enhance the biological effect of the starting natural molecules. Moreover, the species *H. brasiliense* contains 13-hydroxy-8,9-dehydroshizukanolide and rosmarinic acid, both known to exert relaxant, antinociception effects and neuroprotective implications through *in vitro* and *in vivo* assays, suggesting potential application in the treatment of Alzheimer disease. Flavonoids, kaempferol derivatives and neolignans in particular, are very important natural molecules with several health implications and applications that, nowadays seems to be still underinvestigated in *Hedyosmum* genus, although phytochemical investigations performed so far do not pointed out the genus as a source of derivatives particularly rich in this chemical compounds. In light of this lacking data, phytochemical quali/quantitative analysis represents an interesting and promising challenging for the research about *Hedyosmum* genus.

Concerning the EOs from *Hedyosmum* genus, 11 species have been investigated regarding the chemical characterization but only 3 also showed preliminary studies regarding biological activities. As already reported for other research perspectives about *Hedyosmum* species, further research are needed and, in particular, the bioautography-guided approach represents an interesting tool in order to rapidly and easily match phytochemistry and biological activity of phytocomplexes, as shown by Guerrini et al. (2016), and Murakamy et al. (2017). Again, *H. brasilense* is the most investigated species also for its EO, but interesting preliminary results have been reported for *H. sprucei*, especially concerning the cytotoxic activity, suggesting further in-depth investigations. The number of *Hedyosmum* species studied for their essential oil compared to the total of species taxonomically characterizing the genus evidences a wide area of further possible investigation focused on all these aromatic species.

For all these reasons, in order to expand the knowledge and promote the research on the *Hedyosmum* species, the following approaches could be of interest for driving the research community: (1) recollect and systematize the traditional knowledge concerning the *Hedyosmum* species developing specific ethnopharmacological research; (2) design new studies concerning the semisynthesis or the partial chemical synthesis for the development of new bioactive chemical entities based on the bioactive compounds mentioned in Table 5, maybe prioritizing 13-hydroxy-8,9-dehydroshizukanolide (16) and podoandin (11) which have been investigated more than the other molecules; (3) increase the investigation related the use of *H. brasiliense* extracts, fractions or pure compounds as a potential treatment of Alzheimer disease; (4) screen the effective pure compounds of the EOs of the *Hedyosmum genus* with biological activity, privileging the bioautography-guided approach; (5) performing toxicological evaluation (acute and long-term toxicity studies) given the empiric and scientific lacking of these data, except for the vernacular knowledge due to the traditional long term use; (6) more investigations are needed to elucidate the biosynthetic pathways, the pharmacodynamics and pharmacokinetics, the mechanism of action and the toxicity of *Hedyosmum spp*. derivatives.

Based on the current research collected in the present review, most of the pharmacological effects of *Hedyosmum spp*. derivatives can be attributed to their sesquiterpenes, sesterterpenes and hydroxycinnamic acid compounds. The findings showed in the present review mainly focuses on the chemical characterization of pure compounds or EOs from species belonging to *Hedyosmum* genus with different approaches and different in-depth levels; moreover, biological evidences of *Hedyosmum* spp. derivatives are "limited" to *in vitro* and *in vivo* assays and often they did not adequately match the species phytochemically investigated.

All these findings encourage an in-depth investigation focused on *Hedyosmum* genus, which is undoubtedly of great interest in the medical field if we consider the number of existing studies reporting various useful biological activities and chemical characterizations. Most of these studies have been inspired by traditional uses in ethnomedical practices carried out mainly by South and Central America populations.

Due to the importance to develop new bioactive compounds, this review provides a complete and up-to-date overview of traditional uses and scientific studies regarding the *Hedyosmum* genus and represents a starting point for researchers who want to approach the study of these plants from new points of view.

Conflict of interest

The Authors declare that there are no conflicts of interest.

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Author contributions

MR drafted the manuscript, coordinated the study and revised the final version. AT, AP, KDS, and PB participated in data mining, literature analysis and manuscript editing. GS contributed to complete the taxonomical information and revised the final version. SM contributed to the conception of the study. SV and AB monitored the study, revised the manuscript and redacted the final version. All authors reviewed and approved the final version of manuscript.

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